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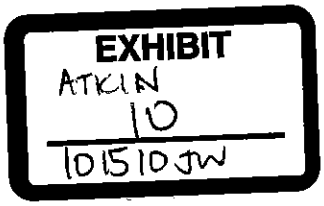
Mesotrione / CALLISTO

A new herbicide for pre- and post-emergence, broad spectrum, broadleaved weed control in maize crops

Request for the Approval of Release for 1st Sales Executive Summary



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Project Description and Commercial Overview

Project Description

Active Ingredient	Mesotrione	
Formulations	YF 11645	100 g/l with built-in-wetter
	WF 2795	480 g/l
Crops	Maize	
Countries	YF 11645	European Union plus Switzerland
	WF 2795	USA, Canada, AME except for Switzerland
Trade Names	CALLISTO	
AI categorisation	Growth	

Commercial Overview

Launch Timetable

2001-2004	Launch of CALLISTO for the post-emergence sector, starting with Germany and Austria (YF11645) in 2001. There is also a less than 50% chance that registration will be achieved of WF2795 in USA in time for first sales in 2001
2003-2006	Introduction of mixture products, primarily for the pre-emergence sector

Objective

To achieve 35% share of the post-emergence target segment by 2005, realising sales of $130M, with gross margin of $100M.

To rebuild a strategy for the pre-emergence sector using Syngenta a.i partners, targeting for first commercialisation in 2003, and building to sales of $140M in this sector by 2007.

Use mesotrione to help build the strongest corn crop package in the USA and European markets and to rationalise Syngenta portfolio.

Strategy

Gain USA and EU Registrations by end of 2001, where possible (prioritise USA, France, Netherlands, Belgium).

Plan a full scale European and USA launch for 2002

Build brand image and external grower awareness in key markets, establishing the CALLISTO brand and Mesotrione as a unique active ingredient

Price in the post-emergent sector to capture the full value of the product, while taking significant market share

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Develop mixture products to exploit the pre-emergence opportunity for first sales in 2003

Decide long-term corn portfolio, taking account of mesotrione

Review opportunity outside Europe and USA in 2001

Review opportunity in other crops in 2001

Product Positioning

CALLISTO is:

A unique corn herbicide developed from nature, which provides

Unprecedented broadleaf weed control

Freedom to apply at any time, as needed in the farmer's weed management programme

Environmental, crop and human safety

Financial Projections

The forecasts for Mesotrione have not been revised by the regions since mid 1999, and the volumes and prices below reflect a 'top down' view from Product Line, Selective Herbicides.

Gross margins are anticipated to be over 70% for CALLISTO brands and over 60% for the mixture products, giving an average for the active ingredient total over 65%.

Total Mesotrione

US $ million	2002	2003	2004	2005	2006	2007	2008
USA	17.7	91.1	131.0	163.9	171.5	181.8	183.6
Mexico + Canada		0.5	1.3	4.0	7.1	8.0	8.1
NAFTA	17.7	91.6	132.3	167.9	178.6	189.8	191.7
France	4.5	9.2	20.1	25.0	25.6	24.7	24.0
Germany	4.3	7.6	10.7	13.4	14.3	14.8	14.9
Italy	1.8	2.6	3.8	6.6	7.6	8.1	8.6
Rest West Europe	5.3	7.6	10.0	13.7	14.2	14.8	14.5
Total WEU	15.9	27.0	44.7	58.7	61.7	62.5	62.0
East Europe	1.7	5.7	11.1	15.2	17.4	18.3	19.0
Switzerland	0.5	1.2	1.5	1.5	1.5	1.4	1.4
South Africa	1.6	2.3	4.3	5.6	6.1	6.6	6.5
Rest ME & Africa	0.3	0.6	1.5	2.1	2.5	2.7	2.6
Total BI	4.1	9.8	18.4	24.4	27.5	29.0	29.4
China			0.8	1.6	2.3	2.2	2.1
Rest AP							
Total AP			0.8	1.6	2.3	2.2	2.1
Brazil			2.1	5.0	6.6	7.3	7.1
Argentina		0.2	1.6	2.7	3.3	3.4	3.5
Rest of LATAM			0.6	1.1	1.5	1.8	1.9
Total LATAM		0.2	4.3	8.8	11.5	12.6	12.5
Total	37.7	128.7	200.5	261.4	281.6	296.1	297.7

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SWOT

Strengths:	Weakness:
■ Technical profile: broad spectrum, flexibility, crop safety ■ Environmental and toxicological profile ■ Cost competitiveness ■ Complementary fit with rest of Syngenta portfolio (esp S-MOC and triazines) ■ High Syngenta competence and market leading position in maize	■ IP position, competitive mixtures patents ■ Not easy to formulate ■ Need for management of Ames issue in production
Opportunities:	**Threats:**
■ Pre-emergence sector in mixture with S-MOC ■ Expansion outside WEU and USA, using synergy with atrazine	■ Strong brand position of Mikado ■ Roundup Ready maize expansion ■ Lack of acceptance of technical positions by regulatory authorities

Market Overview

The maize herbicide market is estimated to be $2350 m at ex Syngenta level, with Syngenta taking 33% share. The market is not expected to see significant change in the next 5 years, with the exception of increased HTC acreage. Total corn acres, crop prices, herbicide treatment acres are expected to show some very modest, but not significant, improvement. HTC penetration will only impact mesotrione in the USA in the next 5 years, and owing to the need for early weed control in corn, the impact on the pre-emergence sector will be moderate. In the USA, total penetration is expected to increase to 25% by 2007, and forecasts have taken account of this.

Competitors

Principal competitors for mesotrione are flumetsulam, dicamba (USA), sulcotrione (Europe), isoxaflutole (USA + Europe) and our own products. Mesotrione has advantages over these compounds of greatly superior flexibility and better crop safety (dicamba and isoxaflutole). It will also be cost competitive. Mesotrione has no important weaknesses compared to the competitive products.

There are no new conventional products expected in the next 5 years, of serious concern.

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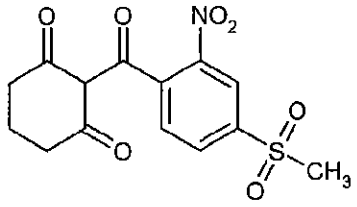
Chemistry

Active Ingredient: **Mesotrione (ISO proposed common name)**

Structural Formula:



Molecular Formula: C14H13NO7S

Molecular Mass: 339.3

Chemical Name: IUPAC: 2-(4-mesyl-2-nitrobenzoyl) cyclohexane -1,3-dione
CAS: 2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1-3-cyclohexanedione

CAS Number: 104206-8

Physico-Chemical Properties

Property	Findings
Melting point	Melting point: 165.3°C with decomposition (Decomposition evidenced by dark red colour and vapour evolution)
Temperature of decomposition of sublimation	Some decomposition on melting at ~165°C
Relative density	1.49 g/mL at 20°C
Vapour pressure	$<5.7 \times 10^{-6}$ Pa at 20°C
Henry's law constant	$<5.1 \times 10^{-7}$ Pa^{-m3}/mol at 20°C
Colour and physical state	Pale yellow solid at room temperature
	Light tan or sand coloured opaque solid
Odour	Odourless
	Slight odour, sweet (not pungent)
Solubility in water	at 20°C: 0.16 mg/mL in unbuffered water 2.2 mg/mL at pH 4.8 15 mg/mL at pH 6.9 22 mg/mL at pH 9

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Solubility in organic solvents	At 20°C: methanol ethyl acetate toluene 1,2-dichloroethane acetonitrile xylenes heptane acetone	 4.6 g/Kg 18.6 g/Kg 3.1 g/Kg 66.3 g/Kg 117 g/Kg 1.6 g/Kg <0.5 g/Kg 93.3 g/Kg
n-octanol/water partition co-efficient	log Pow: 0.11 in unbuffered water 0.90 at pH 5 <-1.0 at pH 7 and 9	
Hydrolysis rate at pH 4,7 and 9	Very little degradation of mesotrione occurred during the test period of 30 days (ie less than 10% degradation) in the pH range of 4-9 at both 25 and 50°C. It is concluded that mesotrione at a nominal concentration of 1µg/ml is stable to hydrolysis.	
Direct photo-transformation	The photolysis half-life and rate constant in sterile aqueous buffer solutions at pH7 at 25°C were 83.7 days and 8.40×10^{-3} /day, respectively at 37° 56' latitude local sunlight which is equivalent to 92 days at 50°N No degradates exceeding 10% of the applied radioactivity were observed	
Quantum yield of direct photo-transformation	following irradiation in aqueous buffer at 20°C: 1.3×10^{-4} at pH 4 $<4.6 \times 10^{-6}$ at pH 7 $<1.6 \times 10^{-5}$ at pH 9 Under mid European conditions the environmental half life (t½) is calculated to be between 6.8 days and >23 years depending on seasonal sunlight, depth of water and pH.	
Dissociation constant	Pka 3.12 at 20°C	
Estimated photochemical oxidative degradation	Atmospheric half-life of mesotrione by AOP under average atmospheric conditions was estimated as 1.5 days.	
Flammability	Mesotrione did not propagate combustion and is therefore not classified as highly flammable in terms of burning	
Auto-flammability	The relative self-ignition temperature of mesotrione is 144 ± 5°C.	
Flash point	Not required since the melting point is >40°C	
Explosive properties	Mesotrione is not classified as an explosive in terms of its mechanical sensitivity to shock and had a limiting impact energy of >40 Joules Mesotrione is not classified as an explosive in terms of its mechanical sensitivity to friction and had a limiting loading greater than 360 Newtons. Mesotrione is not classified as an explosive in terms of its thermal sensitivity	
Surface tension	aqueous solution, 90% saturated with mesotrione: 72.5 mN/m at 20°C which indicates that mesotrione is not surface active	
Oxidising properties	Mesotrione is not classified as an oxidising agent	

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Biological Performance

Summary

Mesotrione is a systemic herbicide for use in maize, which acts by inhibiting the HPPD enzyme. It is readily taken up by the leaves, shoots or the roots and is translocated in both the xylem and phloem. It can be used both pre- and post-emergence and controls an extremely broad spectrum of broadleaved weeds and some grass weeds, which are important in maize, with excellent selectivity. It is an extremely flexible herbicide with a very wide application window and most sensitive weeds are controlled from pre-emergence applications up to at least the 6-leaf stage, although higher rates are required when used pre-emergence.

The use rates of mesotrione are in the range from 50g ai/ha to 150 g ai/ha for a post-emergence application and 140 to 302 g ai/ha pre-emergence. Practical use rates vary depending on weed spectrum, growth stage and the addition of other herbicides. Mesotrione is also an excellent mixing partner for the key Syngenta maize herbicides s-metolachlor, atrazine, terbuthylazine and nicosulfuron. In particular the synergy demonstrated in mixture with triazines allows significant rate reductions of the triazine component.

Mesotrione controls triazine and ALS resistant weed biotypes and no HPPD inhibitor resistant weed biotypes have yet been discovered.

Soil half-lives under normal agricultural conditions are generally in the range of 5 to 15 days and pre-emergence applications give up to 6 weeks residual weed control. Rotational flexibility is good but some crops such as sugarbeet, peas and beans will require an 18 month period before planting can safely occur.

Initial glasshouse trials and field screens have shown that mesotrione is also well tolerated in cereals, rice, cotton, sugarcane, linseed (flax) and peanuts.

Basic Properties/Mode of Action

Mesotrione acts by blocking the function of the essential plant enzyme p-hydroxy-phenyl-pyruvate-dehydrogenase (HPPD). It is a competitive inhibitor of HPPD and by binding very tightly to the enzyme's active site it prevents the normal substrate (4-hydroxyphenyl-pyruvate) from binding and renders the enzyme inactive.

Mesotrione is classified under the Herbicide Resistance Action Committee mode of action classification as a group F2 herbicide and under the similar WSSA scheme as a group 28 herbicide.

Use Targets

Crop Tolerance

Mesotrione is very safe to maize from both pre- and post-emergence applications. It can be used from pre-emergence of maize until the 80 cm tall stage. No crop injury has been observed from pre-emergence applications at twice the recommended use rate. Post-emergence applications are also very safe to maize, but under adverse conditions (cold and wet), localized bleaching symptoms on maize foliage may be

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observed. These symptoms will rapidly disappear and even when such effects have been observed, no adverse yield effects have been recorded, even at twice the recommended use rate. Some varietal effects have been observed with post-emergence applications but normal use rates still give only low levels of bleaching and do not affect crop yield. Overlap rates on such varieties could cause higher levels of bleaching than would normally be acceptable.

In-bred varieties and sweet corn varieties are more sensitive than hybrids (especially to post-emergence applications) and should be tested locally before any variety specific recommendations are made.

Uses in, peanuts, sugarcane, cotton, rice and cereals are under investigation.

Weed Control

Mesotrione controls an extremely broad spectrum of dicotyledonous weeds, which are important in maize, with the additional benefit of control of some grass weeds (Table 1) by both contact and residual activity. The use rates of mesotrione are in the range from 50g ai/ha to 150 g ai/ha (typically 100 g ai/ha) for a post-emergence application and 140 to 302 g ai/ha (typically 180 gai/ha) pre-emergence. Practical use rates vary depending on weed spectrum, growth stage and the addition of other herbicides.

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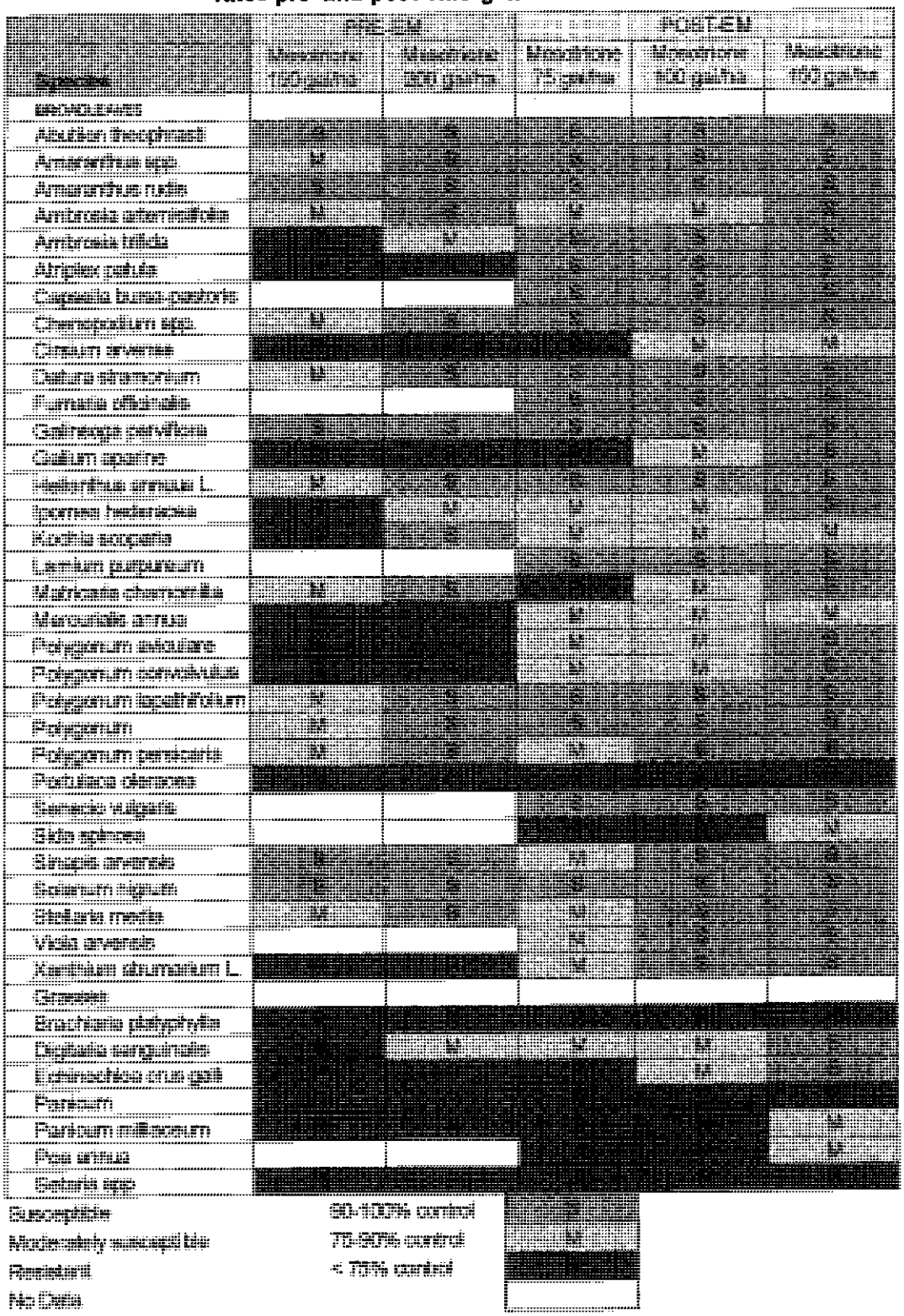
Table 1. Weed control spectrum (key maize weeds) of mesotrione at various rates pre- and post-emergence in maize*



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*The ratings given in the table are typical for the level of control achieved at optimum timings and can only be used as guidance. Local conditions such as weather, soil type and weed growth stage will have an impact on the final level of control achieved and exact use rates will need to be determined locally.

Role of Combination Partners and Additives

Mixtures with triazines

Mesotrione combined with atrazine or terbuthylazine gives synergistic weed control when used post-emergence and allows low rates of the triazine component to be used (250 – 500 gai/ha). In such mixtures the spectrum of weed control is much wider and larger weeds are also controlled. The speed of activity of mesotrione is also enhanced when mixed with a triazine.

Mixtures with S-metolachlor

Mesotrione used in combination with s-metolachlor (Dual) can be applied either pre- or early post-emergence to give season long control of grass and broadleaved weeds in maize. Addition of atrazine or terbuthylazine to this mixture will be useful where weeds such as Xanthium spp. or Ipomoea spp. are present or where longer residual control is required or in difficult conditions to improve the grass weed activity.

Mixtures with nicosulfuron

Although mesotrione has activity on some grass species, the addition of a grass herbicide such as nicosulfuron will give a treatment, offering complete spectrum post-emergence weed control.

Additives

Mesotrione needs to be used with an additive for optimum weed control. In the case of the CALLISTO 100SC formulation this is already built in to the formulation and no further additive is required. The CALLISTO 480SC (4SC) formulation requires additional additive to be used. In post-emergence applications to ensure optimum deposition and uptake CALLISTO 480SC must be used with an additional adjuvant such as COC and it is optional to add an Ammonium source. CALLISTO 480SC should not be used with Methylated Seed Oil as this in combination, especially with an ammonium source, has been shown to be too phytotoxic.

Mixtures / sequences with insecticides

No interactions with any soil insecticides have been observed when mesotrione has been applied pre-emergence. No interactions with post-emergence mesotrione applications have been observed following application of the following insecticides: tefluthrin, chlorpyrifos, fipronil or phosphorothioate + cyfluthrin. Unacceptable crop injury may occur with mesotrione applied post-emergence following applications of terbufos or other organophosphate or carbamate insecticides, which are not mentioned above.

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Side Effects

Effects on Non-Target Plants

Mesotrione is non-volatile (vapour pressure of <5.7 x 10-9 at 20OC) and will not redistribute in the environment as a vapour. Therefore vapour drift is not an issue.

Drift of spray droplets onto sensitive crops (especially dicot crops) could cause very visible bleaching symptoms and care shuld be taken if spraying close to such crops.

Rotational Crop Sensitivity

Glasshouse studies show that certain crops are very sensitive to mesotrione. This means that very low amounts of mesotrione can cause damage to some following crops. Even though the half-life of mesotrione is very short and very low residues of mesotrione are present the season after application these amounts could be enough to cause damage to such sensitive crops. Cultivation, such as ploughing, will help to dilute any residues and will reduce the damage potential but some restrictions may be required depending on the climatic conditions.

Rotational Crop Restrictions

Any rotational restrictions required for mesotrione will be a function of the climatic conditions and the cropping system in question. However, until local trials have been carried out to demonstrate otherwise, the worst case scenario should be taken (table 2). Mixtures or sequences with other HPPD inhibitors (eg isoxaflutole) should not be recommended until we have data to show otherwise.

Table 2. Rotational Restrictions to be Used Until Proven Otherwise Locally

Rotational Crop	Replant if crop failure	Fall (>4 months)	SPRING (>8 MONTHS)	Spring (>18 months)
Maize	OK	OK	OK	OK
Wheat	NO	OK	OK	OK
Barley	NO	OK	OK	OK
Ryegrass	NO	OK	OK	OK
Soybeans	NO	NO	OK	OK
Oilseed rape / Canola	NO	PLOUGH	PLOUGH	OK
Sunflowers	NO	NO	PLOUGH	OK
Beets (all)	NO	NO	NO	OK
Peas	NO	NO	NO	OK
Beans (Phaseolus /Vicia)	NO	NO	NO	OK

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Rotational restrictions – examples

In the US, the rotational crops maize, alfalfa and cereals may be planted 3 months after mesotrione application. Soybeans, cotton, dry beans, tobacco, sugarbeets and sunflowers may be planted 10 months after application.

In Europe the rotational restrictions vary between countries due to the different climatic conditions and cropping systems. In France and Germany, there are no restrictions to maize, cereals or grasses as following crops. Sunflowers may be planted 8 months after the application of mesotrione but ploughing is required. Cultivation of sugarbeets, peas and beans is only recommended 18 months after the application of mesotrione and ploughing is required. There are no restrictions the following season in Italy and Spain.

Additional studies are underway to broaden the rotational options.

Resistance

Status of Resistance

So far there are no recorded instances of resistance developing to HPPD inhibitors (HRAC group F2) and mutagenesis studies with mesotrione have not generated resistant biotypes in over 600,000 mutants.

Risk of Resistance Build-up

As mesotrione is a competitive inhibitor of the HPPD enzyme any mutation causing a change in the enzyme which prevents mesotrione binding, is also likely to prevent the normal substrate binding and would incur a severe fitness penalty. If any type of resistance to HPPD inhibitors does eventually occur, it is likely to be due to enhanced degradation rather than a mutation of the site of action. However this would be unlikely, as resistance caused as a result of enhanced degradation is very rare in broadleaved weeds. In fact mesotrione's novel mode of action aids in weed resistance management. It will control biotypes of weeds, which show resistance to ALS inhibitors or triazines.

Technical Innovation Value

State of the Art (Broadleaved Weed Control in Maize)

Pre-emergence: triazines (atrazine / terbuthylazine), isoxaflutole, flumetsulam

Post-emergence: sulfonylureas (prosulfuron, primisulfuron), triazines, sulcotrione, dicamba, bromoxynil.

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Table 3: Strengths and weaknesses of current standards

Key Competitor Products				
Company	**a.i.**	**Strengths**	**Weaknesses**	**USP**
Syngenta / generic	Triazines	+ broad-spectrum + pre- and post- use + residual activity + some grassweed activity + reliable + excellent fit with acetanilides	– high rate – under regulatory pressure especially in EU – rate restricted in EU and some areas of USA – resistant biotypes of many weeds	* cheap * well known * reliable
Bayer	Sulco trione	+ low rate + grass + dicot activity + new mode-of-action	– post-em only – spectrum gaps on large seeded dicots – not registered in USA – high cost	* new mode-of-action * no groundwater presence * low rate
Aventis	Isoxaflutole	+ low rate + broad-spectrum dicot control + residual activity + controls resistant biotypes + some grass activity	– pre-em only – marginal crop tolerance – no pre-mix available with acetanilide	* controls resistant weeds * Eriochloa control * New mode of action
BASF	Dicamba	+ low rate + dicot activity + some residual	– variable crop tolerance – limited residual – no grass activity	* cheap * other mode of action
Syngenta	Primisulfuron	+ low rate + no carry over + some grass activity	– narrow dicot spectrum – limited residual – ALS resistant biotypes	* sorghum control
Syngenta	Prosulfuron	+ low rate + broad spectrum dicot activity + some residual activity + controls TR weeds	– rate restricted due to carry-over – post-emergence only – ALS resistant biotypes	* flexible timing *
Dow	Metosulam Flumetsulam	+ low rate + dicot activity + some residual	– variable crop tolerance – limited residual – incomplete dicot spectrum	* low rate

Key benefits of mesotrione

- Pre-and post-emergence control of key broadleaved weeds (and some grasses) in maize
- Wide post-emergence application window
- Residual activity
- Controls ALS and triazine resistant weeds
- Low potential for resistant weed development
- Synergy with triazines allows significant triazine rate reduction
- Excellent fit with acteanilides pre-emergence
- Excellent fit with nicosulfuron post-emergence

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Portfolio Fit and SWOT Analysis

- Non-triazine solution for mixture with s-metolachlor +/- triazine in pre-emergence market
- Allows rejuvenation of the pre-emergence product range
- Excellent mixing partner to allow triazine rate reduction
- Excellent fit with nicosulfuron in Europe

Biology SWOT Analysis

Strengths	Weaknesses
■ Wide broadleaved spectrum ■ Good control of Echinochloa and Digitaria post-emergence ■ Residual activity ■ Pre- and post-emergence use ■ Control of ALS and TR resistant biotypes ■ Wide timing flexibility ■ Excellent crop tolerance pre-emergence ■ No varietal restrictions ■ No soil type restrictions ■ Low rate ■ Synergy with triazines ■ Good rotational flexibility ■ New chemistry	■ No Setaria control ■ Rotational restrictions in Europe ■ Slightly higher crop damage potential than Mikado ■ Tolerance in some sweet corn varieties ■ Use of OP insecticides increases the crop damage risk ■ Potential overlaps with prosulfuron, primisulfuron, dicamba and pyridate
Opportunities	**Threats**
■ Replace Mikado in post-emergence market in EU ■ Rejuvenate maize pre-emergence portfolio with S-metolachlor mixtures ■ Streamline maize post-emergence portfolio ■ Use synergy with triazines to manage triazine rates ■ Management of resistant weeds ■ Mixtures with nicosulfuron or foramsulfuron	■ HTC use expands rapidly ■ High quality total post-emergence solution (+ nicosulfuron) takes pre-emergence business ■ New BASF HPPD inhibitor ■ New (currently unknown) competitors are released

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Critical Biological Issues and Actions

Benefits of mesotrione over sulcotrione (Mikado) are small (extra residual, better Amaranthus control) and there are some negatives (crop tolerance, rotational restrictions).

Rotational crop database needs strengthening (especially minor crops).

Development of mesotrione formulations with s-metolachlor require use of mesotrione copper salt. This salt may not be as active as the acid when used post-emergence.

Definition of the threat of the new BASF HPPD inhibitor

Recommendation

Release mesotrione for sales.

References

Mesotrione Biological Profile, Derek Comes, 2001

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Patent Protection

Basic Patents

Syngenta patent protection for compound expires US April 2008, December 2005 most other countries (Mesotrione Patent Portfolio, cases RIA 57307 and RIA 37066). US Patent 5 506 195 covers use of mesotrione as selective herbicide in corn, expires 2014 (RIA 40312).

We know of one third party patent issue;

US 5 318 947 (Hoechst) triketones as rice herbicides.

US Granted 7 June 1994 on a PCT application PCT/EP90/01721 filed 12 October 1990, published as WO91/05470 on May 2 1991. European equivalent EP-0-B 0 496 757 granted in 1995 and covers Italy only. There are also applications in China, Japan and Mexico.

The claims in the US and Europe are similar. They cover a method for controlling harmful plants rice growing which comprises applying to the area under cultivation which contains harmful plants and rice plants or their seeds, one or more compounds of formula (I), or salts thereof, in an effective amount of from 0.001 to 0.5Kg of a.i/ha. Formula (I) broadly encompasses triketones including mesotrione. The invention is alleged to lie in the realisation that relatively low levels of a.i. can be used to control rice weeds. On the face of it, it seems a bit of a thin case on which to base a patent, but they achieved grant in both the US and Europe, so they have the advantage.

The next steps are to (i) check whether the patents are in force everywhere, (ii) order the US and European files to see what they said during prosecution, and (iii) for us to do a search to see if we can find anything which might invalidate their claims. The filing date is quite early, so the relevant art might be quite limited.

Case Number RIA 57307

Priority Date 20/12/1984

Covers 2'-nitro-4'-substituted benzoyl cyclohexanedione (triketone) compounds including mesotrione (CALLISTO, ZA1296). RIA 37066/US/D3 (US 5 006 158) covers mesotrione in the USA.

Case Number RIA 40312

Priority Date 01/11/1994

Use of mesotrione (CALLISTO, ZA1296) as selective herbicide in corn.

Case Number RIA 37066

Priority Date 25/03/1982

Triketones. This case is closely related to both RIA 37448 and RIA 57307.

US divisional D3 (US 5 006 158) covers mesotrione (CALLISTO, ZA 1296), which is covered by RIA 57307 in the rest of the world. US divisional C2 (US 4 780 127) covers sulcotrione and is licenced to Bayer. Sulcotrione is covered by RIA 37448 elsewhere.

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The non-US patents of this case are of limited scope and do not cover sulcotrione or mesotrione.

Supporting Patents

Process of Manufacture

Syngenta patent protection for enol ester rearrangement step ('step 5') expires 2004/5 (RIA 57290). Sold to Bayer in EU and licensed back for all but sulcotrione, licenced to Bayer for Sulcotrione elsewhere.

No known third party patent issues.

Case Number RIA 57290

Priority Date 20/12/1984

An acylated diketonic compound is produced by rearrangement of the corresponding enol ester in the presence of a cyanide source and a molar excess with respect to the enol ester, of a trialkylamine. Covers rearrangement step in process for producing triketone herbicides including mesotrione (CALLISTO, ZA 1296).

EC patents to be transferred to Bayer with sulcotrione and licensed back, and all others licenced to Bayer.

Formulations

Formulations of mesotrione and Crop Oil Concentrate (COC) or Methylated Seed Oil (MSO) with UAN or Ammonium Sulfate (AS) fertiliser covered by recently filed case RIA 57709. Protection may depend on showing of unexpected benefit over prior art and final scope is uncertain at this stage.

BIW formulation covered by recently filed case PPD 50601. Search showed no fatal prior art. Protection may depend on showing of unexpected benefit over prior art and final scope is uncertain at this stage.

No known third party patent issues.

Case Number RIA 57709

Calisto formulations comprising:

(A) mesotrione, (B) 0.3 to 2.5% by volume crop oil concentrate (a petrolium oil/surfactant mixture), or 0.3 to 2.5% by volume of methylated seed oil (C) 0.5 to 5% by total volume urea ammonium nitrate, or 0.5 to 5% by total dry weight of ammonium sulfate fertiliser, (D) a diluent.

Case Number RIA 57679

Method for improving the selectivity,particularly in wheat, of triketone herbicides, including mesotrione, using metal chelates, particularly copper chelates. Also discloses microcapsules of such chelates.

Case Number RIA 57624

Priority Date 02/02/1996

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Chemically stable metal chelates of herbicidal dione compounds. These chemically stable metal chelates of herbicidal dione compounds can be used in liquid formulations or with a liquid carrier, optionally with another agriculturally active chemical.

Covers metal (copper) chelates of ZA1296. These chelates are used for formulation stability in pre-emergent (dilute) mesotrione (CALLISTO) formulations.

Mixtures

Searching has not been carried out for all potential mixtures, and searching is ongoing. There are several known third party mixture patents and applications which might affect our ability to (i) label for tank mixing and (ii) produce pre-mixes.

Case Number RIA 57711

Mesotrione, (2-[4-methylsulfonyl-2-nitrobenzoyl]-1,3-cyclohexanedione), (CALLISTO, ZA 1296), mixtures with glufosinate. CALLISTO + glufosinate mixtures.

Case Number RIA 57618

Priority Date 18/07/1995

A synergistic herbicidal compositions containing a) an herbicidal cyclohexanedione compound and b) an herbicidal chloroacetanilide compound, together with an agriculturally acceptable carrier therefor. The invention also relates to the use of this synergistic composition.

Covers mesotrione (CALLISTO, ZA1296) + acetochlor. Acetochlor is a Dow procuct. The US patent is licenced to Dow, where they must buy our mesotrione for their mixtures.

Case Number RIA 57322

Priority Date 06/07/1987

Herbicidal compositions containing an acylated 1,3-dicarbonyl herbicide, e.g., a triketone herbicide, and an antidote or safener therefor. Herbicide definition is broad and includes mesotrione. Safeners disclosed include amides of haloalkanoic acids, aromatic oximes, thiazole carboxylic acids and 1,8 naphthalic anhydride. US claims limited to these amide and anhydride safeners.

Case Number RIA 40062

Priority Date 22/04/1994

A synergistic herbicidal composition comprising (a) 2-(2'- nitro-4'-methylsulfonyl-benzoyl)-1,3-cyclohexanedione or 2-(2'-nitro-4'-methylsulfonyloxybenzoyl)-1,3-cyclo-hexanedione and (b) 2-chloro-4-ethylamino-6-isopropylamino-S-triazine. Also disclosed is a method of controlling undesirable vegetation by applying an effective amount of such composition to the locus of the vegetation to be controlled.

Mesotrione (CALLISTO) (or the corresponding 4-methylsulfonyloxybenoyl compound) and Atrazine mixture.

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Conflicting Patents

US 6 069 115 (Aventis, Pallett)

Applying post-em mixtures of Glyphosate and HPPD inhibitor over glyphosate resistant crop. A potential problem for labelling for glyphosate mixtures post-em over HTC.

No direct-hit prior art found. Our own application on glyphosate resistance (PPD 50197) is being amended to provoke interference.

Prior art on use of glyphosate alone has been sent to White & Case (external counsel).

US 6 046 134 (DuPont, De Gennaro)

Mixtures of mesotrione and specified sulfonylureas. A potential problem for labelling for nicosulfuron mixtures.

Equivalent WO 97 48276 (= EP 915 652) is still pending with similar claims as in the US. There has been no EP prosecution as yet. No translation has yet been filed in Italy, Germany, France or Belgium, so no provisional protection yet applies there. There is no Canadian equivalent.

We plan to negotiate with DuPont on this. Travis Dickinson sent a letter to them and we are evaluating their reply and planning our response.

US 5 441 922 (Hoechst)

Relevant to mesotrione/cloquintocet-mexyl.

Granted US patent; Mixtures of 2-acylated 1,3 dicarbonyl compounds (generically includes mesotrione) and safener (specifically mentions cloquintocet-mexyl [1-methylhexyl (5-chloroquinolin-8-yloxy) acetate], in a long list on column 13, B2-1). Are other cloquintocet salts / esters covered or just the mexyl?

Granted EP 551 650 includes only safeners of type B1 and so does not cover cloquintocet. But there is a pending divisional, EP 943 240, which covers safeners of type B2 which would, if granted as filed, cover the cloquintocet-mexyl mixture. There has been no prosecution of the divisional as yet.

We will prepare an invalidity argument for this case. We will need more prior art and hence initiate searches.

WO 00/30447(Aventis)

Priority 21.11.98. Relevant to benoxacor and cloquintocet-mexyl.

Very broad claims in this pending application. The application is still in the international phase. Covers mesotrione in mixture with safeners, including cloquintocet-mexyl, isoxadifen, benoxacor. The International Search Report cites many novelty-destroying references, but it is hard to predict exactly what might be granted.

Further searching is still required on some mixtures.

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Strengths	Weaknesses
■ Patented AI ■ SPC in Europe should give AI protection to 2010. ■ Patented copper chelates to 2017 ■ Patent application on BIW formulation. ■ Patented enol/ester rearrangement process. ■ Patented mixture with acetochlor or metalochlor to 2016 ■ Patented mixture with Atrazine to 2014. ■ Patent application on glufosinate mixture	■ AI protection runs out US April 2008. ■ No amount of formulation of mixture patenting can prolong basic patent cover ■ Process patent runs out 2004/5
Opportunities	**Threats**
■ possibility of patent protection for further formulations and mixtures.	■ Several known potential patent problems on use on rice, on mixtures with glyphosate, SUs and some safeners. ■ Need further searches on future mixtures and formulations ■ Third party patent activity on mixtures as yet unpublished.

References

Mesotrione Patent Portfolio, March 2001

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Manufacturing

Summary

Mesotrione will be manufactured in a new, purpose built unit at Syngenta's Cold Creek, USA site. Key chemical intermediates will be sourced from custom manufacturers and outside suppliers, while the final two stages of manufacture (chlorination and condensation/rearrangement reactions) will be performed in a batch manufacturing unit with nameplate capacity of 820 tonnes per annum. This type of manufacture is the heartland of Cold Creek's capabilities. Commissioning activities are underway and commencement of manufacture is envisioned for April 2001.

Two formulations will initially be manufactured for sale in the 2001 and 2002 seasons:

1) a 4 lb/gal SC for NA, Eastern Europe and LATAM, to be produced in a new formulating and packaging unit at the Omaha Nebraska site;

2) a 100 gram per liter SC with built in wetter for Europe, to be toll produced at Safapac in the U.K.

In December 2000, Safapac commenced manufacture with mesotrione technical supplied from the Cold Creek Pilot Plant. Production is currently ongoing to meet the European sales demands in 2001, as country registrations will allow. Omaha will commence manufacture in May 2001 utilizing mesotrione technical from the new Cold Creek unit.

A combination of deep technical knowledge of the mesotrione process, coupled with practical experience gained from pilot plant and other Syngenta products manufacture, provides a solid basis of confidence in the start-up and ongoing production of mesotrione. Additionally, an extensive program of formulation testing, including full season supply chain tests, provides a degree of confidence across the development of the whole product.

Overview

Mesotrione a callistemone compound, will be manufactured in a new, purpose built unit at Syngenta's Cold Creek, USA site. Key chemical intermediates will be sourced from custom manufacturers and outside suppliers. The final two stages of manufacture (chlorination and condensation/rearrangement reactions) will be performed in a computer controlled batch sequence unit, with nameplate capacity of 820 tonnes per annum. Manufacture will commence in April 2001.

Volumes for the launch in 2001 in Europe are currently being manufactured in a pilot plant at Cold Creek.

Two formulations are currently available

1) WF2795 for NA, Eastern Europe and LATAM, to be produced in a new formulating and packaging unit at the Syngenta Omaha Nebraska site;

2) YF 11645 for Europe, to be toll produced at Safapac in the U.K. Options for siting this formulation in-house for the 2002 season are currently being explored.

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In December 2000, Safapac commenced manufacture with mesotrione technical supplied from the Cold Creek Pilot Plant. Over 30,000 liters have been successfully produced to date. Production is ongoing to meet the 2001 demands of Germany and Austria and other European countries as registrations allow. Omaha will commence manufacture in May 2001 utilizing mesotrione technical from the new Cold Creek unit. The commercial launch of the premix will likely not proceed and the capital project at St. Gabriel has been placed on hold. Variations with s-metalochlor are under development as a likely replacement.

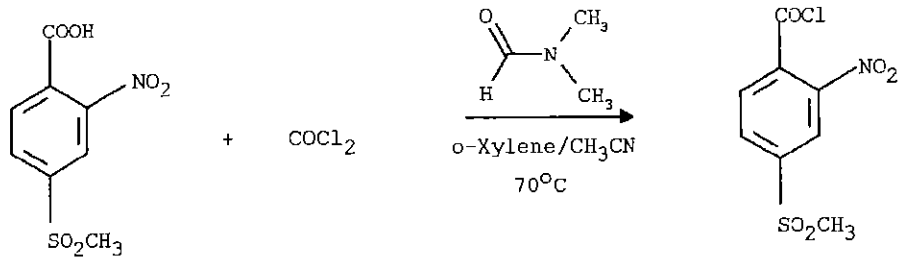
Process Description

Mesotrione, one in a class of callistemone compounds that Zeneca developed in the 1980/90's, is 1,3-cyclohexanedione, 2- [4-methylsulfonyl - 2 nitrobenzoyl]; (Formula Weight = 339.32; Empirical Formula = $C_{14}H_{13}NO_7S$). In the mid 1990's, the Process Technology Department had developed a 'back integrated' process (Stages 1 & 2) to make the NMST using p-toluenesulfonylchloride as the starting material. However, capital considerations favored the decision to source NMST from a custom manufacturer, while limitations on in-house oxidation technology suggested that conversion of NMST to NMSBA (Stage 3) would be better placed at a custom manufacturer. While only the two final stages of manufacture remain in-house, Syngenta has worked closely with its suppliers to create an integrated supply chain. The technology employed is well understood and in the event of a force majeure, transferable to Syngenta. The Process Chemistry for all stages is provided in Attachment 1; the reaction chemistry to be employed at Cold Creek is shown below.

Reaction Scheme

The manufacturing route of meostrione, which utilizes 2-nitro-4-methylsulfonylbenzoic acid (NMSBA) as the starting material, is a batch process involving two reactions:

1. Acid Chloride Reaction (Stage 4)



4-(Methylsulfonyl)-2-Nitrobenzoic Acid | Phosgene | Dimethyl Formamide | 4-Methylsulfonyl-2-Nitrobenzoyl Chloride

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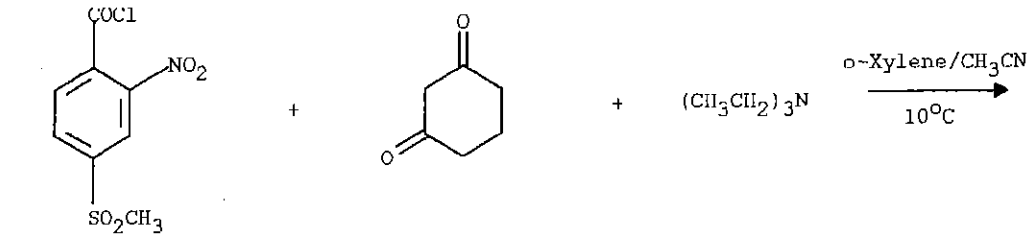
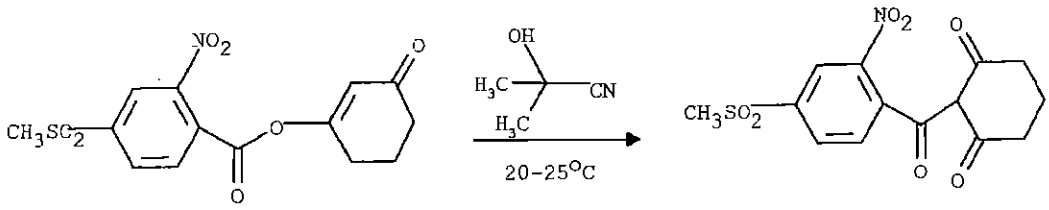
2. Condensation/Rearrangement Reaction (Stage 5)



4-Methylsulfonyl-2-Nitrobenzoyl Chloride | 1,3-Cyclohexanedione | Triethylamine



Enol Ester | Acetone Cyanohydrin | ZA1296

Impurities and By-Products

A potential for the formation of halogenated dibenzo-p-dioxins, halogenated dibenzofurans, polyhalogenated benzenes or biphenyls is not envisaged at any reaction stage. Analysis has confirmed the theoretical prediction that N-nitrosamine formation is highly unlikely. Impurities, which demonstrated activity in the Ames test, have been reduced to insignificant levels by process modification. A complete discussion, including impurities found in mesotrione, is provided in Attachment 2

Initial samples of mesotrione exhibited positive activity in the Ames test. This activity was shown to be due to the presence of xanthenone impurities, in particular,1-cyano-6-(methylsulfonyl)-7-nitro-9H-xanthen-9-one. Process modifications have been introduced, specifically targeted to minimize the xanthenone precursor 2,5-dinitro-4-(methylsulfonyl)-benzoic acid by base washing the Stage 3 intermediate and adding additional purification steps of NMSBA. These modifications and purification steps have been shown to reduce the levels of impurities in technical mesotrione to below the levels of toxicological significance. Upon completion of the pilot plant production campaign where every batch has been Ames tested, characterization using the standard of a five batch sample will be performed to demonstrate the robustness of the purification process.

Registration Specification

CSF392.pdf

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Process Safety / Risks

Mesotrione a.i., and the acid chloride intermediate exhibit thermal instability under certain conditions. The stability of the mesotrione a.i. in ensured by maintaining a minimum moisture content (it is shipped to formulation sites as a wet paste) and storing it at ambient temperature. The acid chloride intermediate stability is maintained by dilution with solvents and limiting temperatures during processing.

All process and storage areas are designed with secondary containment for process leaks as well as storm water run-off. Automatic sprinkler systems are installed throughout the process area to contain and extinguish fires.

Industrial Hygiene / Worker Safety

The mesotrione process utilizes several raw materials and intermediates that are potentially toxic to workers:

- Phosgene – a lethal gas causing pulmonary edema
- Acetone cyanohydrin – evolution of hydrogen cyanide causing cyanosis
- Dimethyl formamide – a suspect carcinogen
- NMSBA – preliminary reports of skin rashes (from vendor)

The Cold Creek site has manufactured phosgene and handled dimethyl formamide and various cyanide compounds for many years. A sophisticated system of process interlocks, backed up by fugitive vapor collection systems is in place to prevent leaks of these materials. In addition, there are specific personal protective equipment (PPE) requirements for tasks such as maintenance line entry, loading/unloading and spill clean-up to prevent incidental exposure to toxic materials.

In the case of phosgene, the site also has an extensive array of fixed leak detection monitors and all personnel are required to wear personal detection badges when within phosgene manufacture/use areas.

Ecology

The mesotrione process produces 30.8 lbs (3.56 gallons) of aqueous wastewater per lb (a.i.) of mesotrione. This consists of 6.5 lbs of aqueous phase from the solvent recovery step, 7.5 lbs of spent scrubber caustic and 16.8 lbs of filtrate and wash water from product separation. These streams require extensive pretreatment prior to discharge to the Wastewater Treatment Plant (WWTP) at Cold Creek. Pretreatment steps include steam stripping of the filtrate and wash water stream to recycle triethylamine (TEA), thermal hydrolysis of all three streams at 170°C to destroy cyanide compounds followed by carbon column treatment to reduce brine color and finally, biotreatment. Detailed descriptions are provided in Attachment 4.

Handling / Transport / Storage

The key raw materials used at Cold Creek to produce technical mesotrione are listed below. Phosgene and Acetone cyanohydrin (catalyst) are lethal service chemicals.

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Raw Material	Form	Container	Shipment Method	Storage
NMSBA	Dry powder	Super Sacks	Sea freight	Warehouse
1,3 cyclohexane dione	Dry powder	Plastic lined Fiber Drums	Sea freight	Refrig. Whse
Phosgene	Gas	Pipe line	Produced on site	none
dimethylformamide	Liquid	Drums	Truck	Warehouse
Acetone cyanohydrin	Liquid	Bulk, 1000 gal deliveries	Rail Car	Bulk Tank
Solvents (acetonitrile, xylene, triethylamine	Liquids	Bulk	Tank Truck	Bulk Tanks

Availability of Raw Material

NMSBA is currently being sole sourced under contract from Nordic Synthesis AB (Sweden) whose capacity is only ~20% of our future requirement. A purpose built unit is under construction at Clariant SA (France) whose capacity will match that of our Cold Creek unit. Clariant is scheduled to commence supply in Q4 2001. All other materials are available from more than one supplier.

Manufacturing Facilities

A $47M capital proposal was approved to construct an 820 tonnes /yr mesotrione unit at Cold Creek Alabama (this sanction amount includes $4.5M to expand formulation and packaging facilities at Omaha and St. Gabriel). Key process equipment in the new plant includes: a 5000 gallon glass lined batch phosgenation reactor; a 2000 gallon coupling/rearrangement reactor; on-site solvent recovery for TEA, xylene, and acetonitrile; and waste water pre-treatment including alkaline hydrolysis for cyanide destruction and carbon adsorption for color removal. The unit is an open structure, four floors high containing 10+ miles of piping, and 700 instrument loops. It will be batch sequence controlled using two, Siemens PLC's. Construction at Cold Creek is complete and commissioning activities are underway. Extensive process development and pilot plant manufacture provide Cold Creek with a high measure of assurance that start up will go smoothly.

Process Patent Situation

There are a number of patents and patent applications (28) for various intermediates (e.g., substituted benzoic acid derivatives) and process steps. We have freedom to operate based on an IP review that was conducted ~18 months ago.

Critical Issues

Start-up of any new facility involves risks including project timing delays, technical uncertainty, mechanical integrity, and raw material supply interruption. Zeneca Engineering completed a Business Interruption Risk Analysis in 2000. Appropriate actions were taken to conform with internal insurance standards.

Risks to manufacture, which are being managed include:

- Poor technical performance that could impact yield, throughput, or quality has been mitigated through the large body of process development

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experience Syngenta has in callistemone chemistry which includes: a) manufacture of sulcotrione at Huddersfield; b) manufacturing steps which are analogous to other products produced at Cold Creek; and c) extensive pilot plant manufacturing experience

- Formulation robustness in every aspect has been assured through an extensive testing program of final products, including large scale supply chain tests
- The Ames impurity issue is a risk to the supply chain. While all the impurities responsible for the Ames response have not yet been quantified, the mechanism for their formation and a process for their removal, are fairly well understood. A process has been implemented which has been shown to be effective in bringing the impurities to acceptable levels. Ongoing Ames testing presents the supply chain with an inconvenient, and time consuming Quality Assurance requirement. Failure of the Ames test will result in product being reworked at an ~10% cost penalty. Depending on the timing of the U.S. registration, the lengthy Ames test could delay the release of mesotrione, potentially resulting in the loss of early U.S. sales in 2001. A decision will be taken shortly, to define the ongoing testing requirements
- Uncertainty around the mechanical integrity (a concern with any new facility) has been mitigated by the large body of technical expertise both in the detail understanding of the process, and deep engineering knowledge relating to equipment applications
- Raw material supply interruption has been addressed by establishing an adequate supply of stocks to enable the unit to run through the commissioning period. One exception is NMSBA supply, where interim use of St Gabriel's MPF unit is required to underpin purification capacity for our single supplier. St. Gabriel manufacture is underway. Longer term, a second source of supply has been identified and approved whose capacity will meet Syngenta's nameplate capacity.

Conclusion

The manufacturing process for mesotrione is well understood, and the newly constructed plant has been built to high standards. With the experienced Cold Creek manufacturing team in place, the safe and timely start up (and ongoing operation) is considered to be within the normal practice of manufacture within Syngenta and should commence in April 2001 as planned. Robustness of the formulations should allow us to go into the launch season with confidence.

References

Description of Process Chemistry: T. Truncellito, 2001

Discussion of Formation of Impurities. T. Truncellito, 2001

Waste Treatment and Disposal. Ch. Edmunds, 2001

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Human and Animal Safety Evaluation

Impact on Human and Animal Health

Summary

When administered orally to the rat and the mouse, mesotrione is excreted rapidly in the urine, mainly unchanged.

Mesotrione is not acutely toxic. The oral and dermal MLDs in the rat are greater than 5000 mg/kg and 2000 mg/kg, the respective limit doses for the studies. It produces little irritation to the skin and eyes of rabbits and is not a sensitizer of guinea pig skin. The no-effect level in a rabbit 21 day sub-acute dermal study was 1000 mg/kg/day, the highest dose tested.

Mesotrione was not teratogenic in the rat, rabbit or mouse at 1000, 500 and 600 mg/kg/day, the highest doses tested, respectively. There was a low incidence of litter losses in the rabbit at the high doses of 250 and 500 mg/kg/day; a slight reduction in foetal bodyweight was observed in the rat at the limit dose. Small differences in skeletal ossification were observed at a range of dose levels in the rat and to a lesser extent in the rabbit. In the rat the changes were dose related but seen in the presence of maternal toxicity, while in the rabbit the differences showed no strong relationship to dose. A marginal difference from control was also seen in the mouse but only at the highest dose tested. Such minor shifts in ossification are transient in nature and are considered not to be of toxicological significance in terms of post-natal development.

Mesotrione did not affect reproductive performance in the rat at 2500 ppm in the diet (equivalent to approximately 280 mg/kg/day) nor or in the mouse at 7000 ppm (1400 mg/kg/day), the highest doses tested in both cases. In the rat the no-effect level for ocular, kidney and litter parameters was 2.5 ppm in the diet. The no-effect level for all parameters in the mouse study was 350 ppm in the diet, equivalent to approximately 71 mg/kg/day.

No-effect levels have been established over both 90 days and one year in the mouse at

350 ppm in the diet (equivalent to approximately 56 mg/kg/day) and in the dog at 100 mg/kg/day.

Mesotrione was not genotoxic in a range of *in vitro* and *in vivo* assays. Prior to the start of the long-term bioassays, the ability of mesotrione to induce specific hepatic isoenzymes, predictive for hepatocarcinogenicity, at high dietary levels was assessed. Mesotrione was chosen specifically as a compound which was forecast not to produce hepatic neoplasia. It was not carcinogenic in the long-term bioassays at 2500 ppm in the diet of rats and at 7000 ppm (Limit Dose) in the mouse. A slightly higher incidence of lesions in the thyroid gland of rats was not predictive of a carcinogenic response in humans.

The mechanism of toxicity of mesotrione has been thoroughly investigated and mesotrione is of low toxicity in all studies relevant to human risk assessment. In studies in mice, dogs and rabbits mesotrione provides high no observed effect levels (NOELs) with what toxicity there is being characterised by non-specific effects on growth or clinical condition with little or no histopathology findings of toxicological significance. By contrast, in rats mesotrione has been shown to produce ocular opacity, reduced bodyweights, increased liver and kidney weights, reduced pup survival and litter size and an increased incidence of spontaneous lesions, which are common in the strain of rat tested. The changes in the rat are all related to severe

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tyrosinaemia induced by mesotrione in rats and are considered not to be relevant to human risk assessment.

It has been demonstrated that tyrosine is the mediator of the toxic effects in rats and that the species and sex differences in the toxicology of mesotrione are a result of the differences in the disposition of excess tyrosine. Studies in the rat, mouse and humans demonstrate that mice and humans do not develop the severe tyrosinaemia produced in rats. The extensive human database includes clinical data and studies with a more potent HPPD inhibitor sister-chemical of mesotrione, NTBC. NTBC has been developed as a paediatric drug and has been used internationally to help save the lives of over 200 children suffering from a hereditary disease. Additionally, studies have been conducted with NTBC and mesotrione in healthy male volunteers.

To illucidate the mechanism of toxicity, extensive investigative studies with mesotrione have been conducted and have shown that it has a single mode of action in mammals, inhibition of the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD) . A difference in the activity of a second enzyme, tyrosine aminotransferase (TAT), between the rat and the mouse leads to a significantly different toxicological profile in both species. This difference is due to a mesotrione-induced severe prolonged tyrosinaemia in the rat which does not occur in the mouse because of the significantly greater activity of the enzyme TAT in the mouse .

The levels of the key enzyme TAT are similar in both the mouse and man and are significantly higher than in the rat. Therefore, the toxicity seen in the mouse following administration of mesotrione is considered to be predictive of the potential hazard of mesotrione to man, whereas the rat is considered to be an inappropriate model

On the basis of the mesotrione toxicology data base, Zeneca proposed that the following no-effect levels (NOEL), as presented in Table 1.1-1, below, are used for safety assessment purposes.Text

Table 1: Proposals of mesotrione no-effect levels for safety assessment purposes

Study Type		Nature of Main Effects	No-Effect Level
21 Day Dermal		-	>1000 mg/kg/day (limit dose)
90 Day Dietary	Mouse	Small bodyweight reductions & liver weight increases.	350 ppm (equivalent to 62 mg/kg/day)
One Year Dietary	Mouse	Small bodyweight reductions plus liver & kidney weight increases.	350 ppm (equivalent to 56 mg/kg/day)
90 Day Oral	Dog	Small bodyweight reductions & liver weight increases.	100 mg/kg/day
One Year Oral	Dog	Minimal ocular toxicity. Small bodyweight reductions & microcytic polycythemia.	100 mg/kg/day
Reproduction	Mouse	Small bodyweight reductions	350 ppm (equivalent to 71 mg/kg/day)
Developmental Toxicity	Rat	Reduced foetal weight	300 mg/kg/day
	Rabbit	Litter losses	100 mg/kg/day
	Mouse	No significant effects	600 mg/kg/day

Aceptable Daily Intake (ADI) and Chronic Reference Dose (cRfD)

The proposed acceptable daily intake (ADI) and chronic reference dose (cRfD) for mesotrione are both 0.56 mg/kg bodyweight/day, based upon the No Observed Adverse Effect Level

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(NOAEL) in the one year chronic toxicity study in mouse of 56 mg/kg bw/day, and using a 100 fold safety factor.

Acute Reference Dose

The acute reference dose for mesotrione can be set based upon the relevant 90 day NOEL of 350 ppm in the mouse, equivalent to 62 mg/kg/day. This is then applied with a safety factor of 10 for inter-species differences and a factor of 10 for intra-species differences.

aRfd = 62/100 = 0.62 mg/kg/day

This is supported by the results obtained in the oral human volunteer study showing that the acute reference dose for mesotrione is greater than 0.4 mg/kg bodyweight/day based upon the highest dose tested in the oral human volunteer study of 4 mg/kg and a 10 fold safety factor to account for intra-species differences.

Acceptable Operator Limit (AOEL)

Mesotrione will be applied once a year to maize in the EU. Individual growers would therefore be exposed on only a few days during the maize post-emergence period. Whereas contract operators might use the product over a period of eight weeks at a time during April to June. Therefore, the most relevant toxicity NOAEL to take into account for an assessment of toxicological risk to operators, workers and bystanders is that from a sub-chronic 90 day oral dosing study. For mesotrione, this value is 350 ppm (equivalent to 62 mg/kg/day) in the mouse.

The Acceptable Operator Exposure Level (AOEL) is defined as an estimate of the amount of an active substance, expressed on a bodyweight basis per day, that can be absorbed, ingested or inhaled, through occupational exposure without appreciable health risk. This is then calculated by taking account of the mouse oral absorption value of 69% and an assessment (safety) factor of 25. The assessment factor is based upon an inter-species difference of 10 and an intra-species factor of 2.5 chosen with respect to the homogeneity of the agricultural working population.

The AOEL for mesotrione is therefore:

(62/25 x (69/100) = 1.71 mg/kg/day

An AOEL for bystanders can be calculated by taking the same 90 day oral dosing study NOAEL of 62 mg/kg/day adjusted for 69% absorption and an assessment factor of 100 to account for inter-species differences (factor of 10) and for intra-species variation of potential bystanders including all sensitive human sub-populations (factor of 10).

The AOEL for bystanders is therefore:

(62/100) x (69/100) = 0.43 mg/kg/day

Drinking Water Limit

World Health Organisation (WHO) health based standards for drinking water provide a calculation to determine a guideline limit for the maximum concentration in drinking water. On the basis that exposure through drinking water should not account for more that 10% of the ADI, assuming an average consumption of 2 litres of water per person per day and a bodyweight of 60 kg, a parametric value of 1.68 mg/l is proposed.

The parametric value is calculated as:

(0.56 x 0.1 x 60)/2 = 1.68 mg/l

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Where 0.56 mg/kg bodyweight/day is the ADI.

Consumers Risk Assessment

Currently mesotrione will not be applied to maize varieties for human consumption (i.e. sweetcorn) and there are no residues (<0.01mg/kg) in any other relevant commodity, including animal products, the estimated consumer intake levels will not exceed the proposed ADI of 0.56 mg/kg/day. It can therefore be concluded that acceptable margins of safety exist for consumers.

Medical Data

Medicinal Surveillance on Manufacturing Plant Personnel

During the development phase, mesotrione was synthesised in Zeneca Western Research Centre (California). Similarly the active ingredient has been used to formulate product. This work has been restricted so far to small scale semi-technical operations.

An occupational exposure standard (OES) value of 10 mg/m^3 (8-hour TWA). No occupational hygiene assessment data is available as yet.

There are no health surveillance programmes currently being undertaken for mesotrione as there is no confirmed human health risk associated with the compound. However, adverse reactions are recorded following the following procedure.

The Stewardship Department of Zeneca Agrochemicals, which includes the Occupational Health function, has maintained a database of incidents involving chemical exposure of workers since 1983. At the time it was set up, it was used to formally record reports of clinical conditions arising during work at the research station at Jealott's Hill in Berkshire (UK) and formulation plant at Yalding in Kent (UK). Information is gathered at the time of the incident and is recorded on a standard form by the Occupational Health Nurse or the doctor. From the start of 1994, data have been collected from all Zeneca's sites around the world. The information is then collated into a computer database which is searchable by product or by active ingredient.

Searching the database has revealed one report. This was a case where a field trials worker spilled some undiluted product onto his leg and developed a rash. This settled with the standard medical treatment and has not recurred.

Direct Observations

No data from the open literature exists relating to clinical cases and poisoning incidence since this is a new active ingredient on the market.

Diagnosis of Poisoning

There are no reported human poisoning cases with mesotrione, either in the medical literature or in company records.

In animal toxicology studies, no specific signs or symptoms of poisoning with mesotrione have been described. The primary cause of the majority of sublethal symptoms observed are attributable to species specific tyrosinaemia, which is not relevant in humans.

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In cases of human poisoning, it is expected that no specific signs of toxicity would be evident, but that ingestion of significant amounts of mesotrione would result in nausea, vomiting, diarrhoea and abdominal pain.

Diagnosis of acute poisoning with mesotrione should be made on the basis of verified exposure within 2 days before the onset of corresponding symptoms and reasonable exclusion of other diseases.

No analytical methods for the detection of mesotrione or its metabolites in body fluids have been described.

Impact on Human and Animal Health: List of Endpoints

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of absorption:	70% absorption; majority within 36 hours.
Distribution:	Urine and faeces
Potential for accumulation:	Low
Rate and extent of excretion:	Rapid up to 52% of the dose excreted within 6 hours up to 95% of the dose excreted within 72 hours (mouse)
Main animal metabolites	None exceeding 0.1%

Acute toxicity

Rat LD_{50} oral	> 5000 mg/kg
Rat LD_{50} dermal	> 2000 mg/kg
Rat LC_{50} inhalation	> 5 mg/l
Skin irritation	Non-irritant
Eye irritation	Non-irritant
Skin sensitization	Not a skin sensitiser (Magnusson and Kligman)

Short term toxicity

Target/critical effect	Mouse: reduced bodyweight, increased liver weight, minor haematology changes
Lowest relevant oral NOAEL/NOEL	350 ppm (equivalent to 62 mg/kg/day) in the mouse
Lowest relevant dermal NOAEL/NOEL	> 1000 mg/kg/day (limit dose) in the rabbit
Lowest relevant inhalation NOAEL/NOEL	None
Genotoxicity (Annex IIA, point 5.4)	Mesotrione: Negative in vitro (Ames, human lymphocytes, mouse lymphoma) Negative in vivo (mouse micronucleus and UDS)

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Long term toxicity and carcinogenicity

Target/critical effect	Mouse: small reduction in bodyweight, minor increase in liver and kidney weight
Lowest relevant oral NOAEL/NOEL	350 ppm (equivalent to 56 mg/kg/day) in mouse
Lowest relevant dermal NOAEL/NOEL	1000 mg/kg/day in rabbit
Carcinogenicity	Not a carcinogen

Reproductive toxicity

Reproduction	350 ppm (equivalent to 71 mg/kg/day) in mouse
Development toxicity	rat: 300 mg/kg/day mouse: 600 mg/kg/day rabbit: 100 mg/kg/day
Lowest relevant reproductive NOAEL/NOEL	350 ppm (equivalent to 71 mg/kg/day) in mouse

Delayed neurotoxicity

No relevant effects.

Other toxicological studies

Mechanism of toxicity has demonstrated that tyrosine is the mediator of the toxic effects in rats which are not relevant to man. Mouse is a relevant model for human risk assessment.

Medical data

To date, there are no concerns raised by the use of mesotrione by Syngenta personnel.

Summary

ADI (=cRfD)	0 - 0.56 mg/kg bodyweight/day
AOEL	1.74 mg/kg/day
Drinking water limit	1.68 mg/l
aRfD (acute reference dose)	> 0.4 mg/kg/day (human oral study) 0.7 mg/kg/day (90 day mouse)

Dermal absorption

In vitro human skin absorption study: Absorption through human epidermis is predicted to be very slow
In vivo dermal human volunteer study: - used in operator exposure calculations 1% and 3% dermal absorption for mixing and loading and spray dilution, repsectively.

Residues, Pre-Harvest Intervals, Maximum Residue Limits

Summary

The metabolism of mesotrione has been studied in maize. There were no residues of concern and the metabolism of mesotrione in plants was relatively simple, with two metabolites, MNBA and AMBA, and an intermediate, 4-hydroxy mesotrione, being identified. Radioactive residues were highest in maize fodder, with MNBA at 0.019 mg/kg (1.8% TRR) and AMBA and its conjugates at 0.301 mg/kg (28.2% TRR). These two metabolites are, however, not considered to be of toxicological concern.

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Since there are no residues of mesotrione in any relevant animal feeding stuffs, animal feeding studies are not relevant. However, a dairy cow metabolism study was conducted for the main metabolite identified in fodder; AMBA. It was demonstrated that 88.7% of the dose was excreted in the urine and faeces. AMBA residues were <0.01 mg/kg in milk, meat, liver and most body fat. Residues of 0.053 and 0.018 mg/kg were detected in the kidney and perirenal fat, but it should be noted that in this study the maximum calculated daily intake was considerably exceeded (more than 60 times) and no detectable residues are expected after normal field use of mesotrione.

Since there were no significant residues of mesotrione or its metabolites in grain, a hen metabolism study was not necessary.

Definition of Residues Relevant for MRLs

Based on the metabolism of mesotrione in maize, residue for plants, plant products and products of animal origin should be defined in terms of mesotrione alone.

Definition of Residues Relevant to the Environment

In the laboratory under aerobic conditions mesotrione is degraded rapidly in soil to two metabolites MNBA and AMBA. MNBA and AMBA are degraded further into CO_2. Under anaerobic conditions, the major degradation product is AMBA which is further degraded into CO_2.

The results obtained in the laboratory were confirmed under field conditions in European and US dissipation trials. In the European trials, MNBA was only detected in the 0-10 cm horizon in two out of six trials at a maximum level of 0.03 mg/kg and degraded rapidly to below the limit of determination (LOD of 0.005 mg/kg). AMBA was detected in one single trial in 0-10 cm horizon at 0.006 mg/kg and subsequently degraded rapidly. In US field trials, no residues of MNBA or AMBA above the limit of quantitation (0.01 mg/kg) were determined in any sample at any trial. No mesotrione was determined above the limit of quantitation (0.01 mg/kg) below the 6-inch depth, despite precipitation exceeding local averages.

Both MNBA and AMBA have been shown to be of low mammalian toxicity and not to be herbicidally active. They have also been shown to be of low toxicity to aquatic invertebrates.

It can therefore be concluded that MNBA and AMBA are of low toxicological and environmental concerns.

It is therefore proposed that mesotrione residues are the only residues of significance to be reviewed in a risk assessment.

Metabolism

Proposed Metabolic Pathways in Plants and Animals (ZA1296 = mesotrione)

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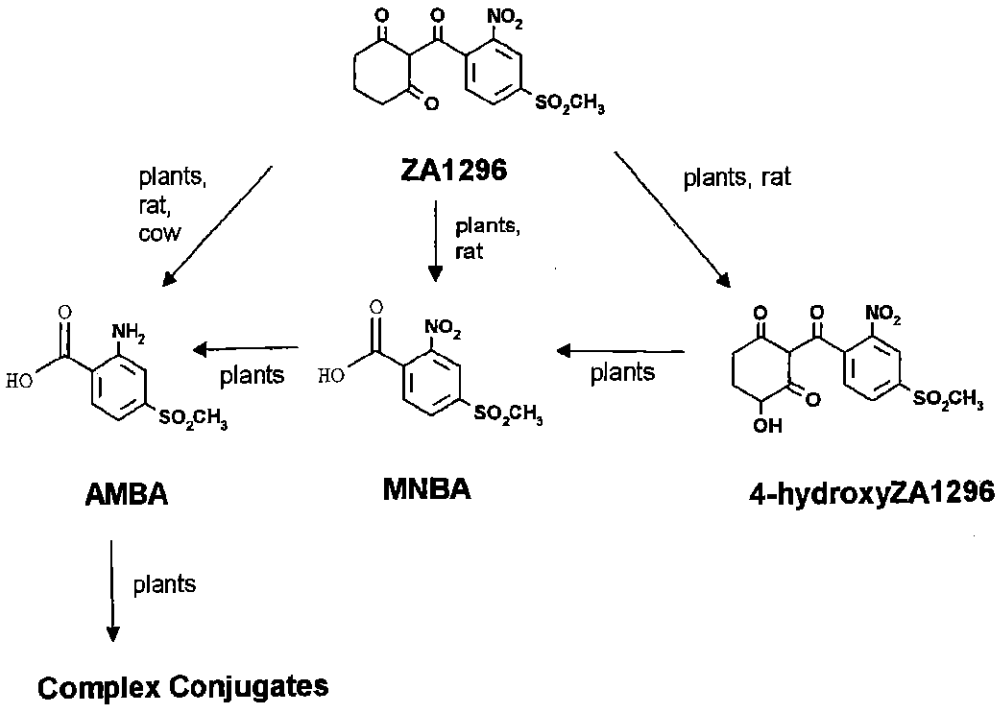

Maximum Residue Limits Pre-Harvest Intervalls

The plant residue definition for monitoring is mesotrione. The tolerance (or MRL) for the relevant commodity, maize grain, is proposed to be set at the limit of quantitation of the residue method i.e. 0.01 mg/kg.

Since there are no detectable residues of mesotrione in animal feedingstuffs (<0.01 mg/kg), a residue definition for animal residues is not considered to be relevant.

References

Mesotrione (ZA1296): Reduced Risk Rational II, Supplement To MRID: 4405002. Drost, D. Kaminski, B.J., Wheals, I.B., March 1999.

Mesotrione (ZA 1296): 91/414/EEC APPLICATION OF ZA1296 M II Section 3/4

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Environmental Safety

Environmental Fate

Summary

The degradation of mesotrione in soil has been extensively studied in both the laboratory and in the field. Mesotrione was rapidly degraded under aerobic conditions to metabolites MNBA and AMBA which were further mineralised to CO_2. Both metabolites were transient with half-lives ranging from 2-10.6 days under aerobic conditions. Under anaerobic conditions the major degradation product was AMBA, accounting for up to 40% of the applied radioactivity.

The degradation rate of mesotrione was rapid in both the laboratory and the field. The laboratory DT_{50} and DT_{90} ranged from 4.5-32 days and 15-105 days with a mean of 15 days and 50 days, respectively. In field studies DT_{50} and DT_{90} ranged from 2-8 days and 26-73 days with a mean of 6 and 40 days, respectively. Field study results were similar in the US with a mean DT_{50} of 9 days (range 2 to 14 days).

The adsorption and desorption studies showed that mesotrione was potentially mobile in soil, however the soil dissipation studies showed no measurable residues (<0.005 mg/kg) of mesotrione or metabolites in soil below 10 cm. The adsorption coefficient of mesotrione varied over a wide range of K_{oc} 14-390 (mean = 108 and median = 70). This was dependent on the pH of the soil with adsorption of mesotrione decreasing with increasing soil pH. This can be explained by a dissociation of mesotrione to its anionic form at high pH. This increases the availability of mesotrione to microbial degradation and mesotrione shows a strong correlation between soil half-life and pH, as shown by decreasing half-life with increasing pH. As a result the potential mobility of mesotrione in higher pH soils is mitigated by a increased rate of degradation.

A strong correlation between both adsorption and degradation rate was demonstrated by measuring K_{oc} and half-lives in the same soils.

Mesotrione is relatively stable to hydrolysis across a wide range of pH (pH 5-9), with less than 10% degradation after 30 days at 25°C, although the anaerobic metabolism study has shown that mesotrione degrades rapidly in flooded systems, with a half-life of approximately 4 days.

Mesotrione degraded rapidly in natural water systems with DT_{50} and DT_{90} ranging from 3-6 days and 10-20 days, respectively. AMBA was the only identified metabolite above 10%. It reached a maximum of 19%, 14 days after incubation.

Mesotrione photolyses in aqueous solution, with a half-life of 92 days at 50°N. No individual photoproduct exceeded 10% of the applied dose, with the exception of CO2.

Mesotrione is not expected to volatilised from soil and leaf surfaces.

Soil

Route of degradation (aerobic) in soil

mineralization after 100 days	Up to 75%
non-extractable residues after 100 days	Up to 37%

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relevant metabolites - name and/or code % of applied (range and maximum)	MNBA (0.7-7.6) mean ≈ 4.0% of applied AMBA (1.8-9.7) mean ≈ 5.0% of applied

Route of degradation in soil - Supplemental studies

Anaerobic degradation	DT_{50} ≈ 4 days DT_{90} ≈ 13 days AMBA up to 40% of applied
Soil photolysis	DT_{50} ≈ 20 days at 50°N

Rate of degradation in soil

Method of calculation	First order kinetic (simple exponential) - laboratory studies Timme and Frehse - field studies
Laboratory studies (range or median, with n value, with r2 value	DT_{50}lab 15 days @ 20-25°C, aerobic (range 4.5-32 days over 18 soils)
	DT_{90}lab 50 days @ 20-25°C, aerobic (range 15-105 days over 18 soils))
	DT_{50}lab (10°C, aerobic): 30 days
	DT_{50}lab (25°C, anaerobic): 4 days DT_{90}lab: 12-14 days
Field studies (state location, range or median with n value)	DT_{50}f: 6 days (mean of 6) (range 2-8 days) France, Italy, Germany
	DT_{90}f: 40 days (mean of 6) (range 21-73 days)
Soil accumulation and plateau concentration	Mesotrione mesotrione degraded rapidly in soil. It does not accumulate.
	DT_{50}: 2 to 14 days (mean 9 days) USA (sites in Illinois, North Carolina, and Mississippi)

Soil adsorption/desorption

Kf/K_{oc}	K_{oc} ranged from 14-390 median K_{oc} = 70, mean K_{oc} = 108
pH dependence (yes/no)	yes

Mobility in soil

Column leaching	Not required
Aged residues leaching	Not required
Lysimeter / field leaching studies	Not required

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Water

Route and rate of degradation in water

Hydrolysis of relevant metabolites (DT50) State pH and temperature) Photolytic degradation of relevant metabolites	There are no relevant environmental metabolites
Readily biodegradable (yes/no)	No
Degradation in -DT50 water water/sediment -DT50 whole system	DT_{50}= 3-6 days (DT_{90}= 10-20 days) same as values in water as mesotrione levels in sediment did not exceed 4% of the applied dose at any point.
Distribution in water/sediment systems (metabolites)	AMBA was distributed in both water and sediment and reached a maximum of 19%, 14 day after incubation.
Distribution in water/sediment systems (metabolites) Field or mesocosm studies	-

Air

Fate and behaviour in air

Direct photolysis in air	Assumed negligible in all risk assessments.
Photochemical oxidative degradation in air (DT50) Volatalization	Atmospheric half-life by AOP = 1.5 days
from plant surface:	<10% volatilisation over 24h
from soil:	<10% volatilisation over 24h

Ecotoxicology

Effects on Aquatic Organisms

The acute toxicity of mesotrione to 3 species of fish, *Daphnia*, mysid shrimp, Pacific oyster, 4 species of algae and the duckweed, *Lemna gibba*, has been determined. Further data on chronic toxicity of mesotrione and acute toxicity of a metabolite of mesotrione, MNBA and AMBA, have also been generated. The data are summarised below.

Table 2-1: Acute toxicity of mesotrione

Duration	Test species	L(E)C_{50}
96 h	Rainbow trout *Oncorhynchus mykiss*	>120 mg/l
96 h	Bluegill sunfish *Lepomis macrochirus*	>120 mg/l
96 h	Mirror carp *Cyprinodon variegatus*	410 mg/l
48 h	Waterflea *Daphnia magna*	900 mg/l
48 h	Mysid shrimp *Mysidopsis bahia*	3.2 mg/l
48 h	Pacific oyster *Crassostrea gigas*	69 mg/l
72 h (120 h)	Freshwater green algae *Selenastrum capricornutum*	4.5 mg/l (3.5 mg/l)

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72 h (120 h)	Freshwater diatom *Navicula pelliculosa*	66 mg/l (66 mg/l)
120 h	Blue-green alga *Anabaena flos-aquae*	54 mg/l
120 h	Marine green algae *Skeletonema costatum*	
14 day	*Lemna gibba*	7.7 µg/l

Table 2-2: Chronic toxicity of mesotrione

Type of study	Test species	NOEC
36 days (32 days post-hatch), flowthrough	*Pimephales promelas*	12.5 mg/l (MATC 18.0 mg/l)
21 day, semi-static	*Daphnia magna*	180 mg/l (MATC 230 mg/l)

Table 2-3: Acute toxicity of MNBA

Type of study	Test species	LC_{50}
96 h	*Oncorhynchus mykiss*	>120 mg/l
48 h	*Daphnia magna*	130 mg/l
72 h	*Selenastrum capricornutum*	38 mg/l

Table 2-4: Acute toxicity of AMBA

Type of study	Test species	LC_{50}
96 h	*Oncorhynchus mykiss*	100 mg/l
48 h	*Daphnia magna*	160 mg/l
72 h	*Selenastrum capricornutum*	9.4 mg/l

As expected for a herbicide the algal species and, in particular, duckweed (*Lemna gibba*), were predominantly the most sensitive organisms.

Since the octanol-water partition coefficient of mesotrione is considerably less than 3, there is no risk of bioaccumulation in fish or aquatic invertebrates.

Effects on Birds

Mesotrione is of low acute toxicity to birds as indicated by the acute oral LD50 value of >2000 mg/kg to bobwhite quail (*Colinus virginianus*).

In subacute (5-day dietary) studies, mesotrione also proved to be of very low toxicity to both mallard duck (*Anas platyrhynchus*) and bobwhite quail. The dietary LC50 concentration was >5200 ppm for both species.

In reproductive toxicity studies in the mallard duck and bobwhite quail, the no observed effect levels were 120 and 3000 ppm respectively (equivalent to 21 and 282 mg/kg bodyweight/day).

Effects on Bees

Mesotrione is of low toxicity to honeybees by both contact and oral routes with the 24 and 48 hour LD50 being >100 and >11 mg ai/bee and can therefore be considered as harmless to bees.

Effects on Other Arthropods

The effect of mesotrione to a range of beneficial arthropods present in the foliage and soil has been studied.

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No ecologically significant effects were seen for *Poecilius cupreus*, *Aphidius rhopalosiphi*, *Aleochara bilineata* and *Chrysoperla carnea* when exposed to mesotrione residues. Mesotrione is therefore classified as harmless (Class 1 of the IOBC categorisation) to these species.

Mesotrione was toxic to *Typhlodromus pyri* with the LC50 of the 100 g mesotrione/l SC being

8.6 g ai/ha and NOEC being 2 g ai/ha. Some toxicity to Pardosa was evident in the laboratory studies, but a field study conducted using the 100 g mesotrione/l SC in 2000 showed no significant effects.

However, when applied at the maximum recommended field rate of 150 g ai/ha, mesotrione is not expected to have any unacceptable long-term effects on exposed on-crop non-target arthropods. Whilst transient effects on some species are possible, there is a high potential for recovery well within one season, due to rapid degradation of the product. Therefore the criterion for authorisation of preparations described in EU Annex VI (Uniform Principles) are considered to be fulfilled.

In relation to the off-crop environment, it is concluded that, under normal conditions of use in the field, there is a very low risk to non target arthropods following application of mesotrione on maize.

Effects on Earthworms

The acute toxicities of mesotrione and the metabolite, MNBA, to the earthworm were studied in the laboratory over 14 days and the no observed effect concentrations for both mesotrione and MNBA were ≥1000 mg ai/kg (dry weight).

Effects on Soil Microorganisms

Mesotrione, applied to loamy sand soil at a rate equivalent to 400 g ai/ha, did not result in any effects on soil microflora respiration or nitrogen transformations in the soil.

Effects on Biological Methods for Sewage Treatment

Use of plant protection products containing mesotrione should not give rise to contamination of sewage treatment works. Nevertheless, a study to determine effects of mesotrione on *Pseudomonas putida*, a micro-organism used as a representative of those which may be present in sewage treatment works, showed no adverse effects at concentrations up to and including 100 mg ai/l.

Effects on Other Non-target Microorganisms

Mesotrione has been thoroughly tested for pre- and post-emergence effects on a wide range of monocotyledonous and dicotyledonous plants. On the basis of the tests conducted, it is concluded that, within the target treatment area, effects on the majority of monocotyledons will be negligible. In contrast, there will be a major risk to dicotyledons due to the specific mode of action of mesotrione.

Adjacent to the treated area, there will be a risk associated with the use of mesotrione to dicotyledonous plants, with negligible potential damage to monocotyledons. Ground application of mesotrione will minimise spray-drift and mitigate some of the potential risks, however it is possible that, in particular, broad-leaved non-target species will be affected at short distances from the target area.

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No screening data are available on effects on non-target invertebrate groups. The results from honeybee, beneficial arthropod and earthworm testing, however, indicate that there is a low potential for risk to non-target invertebrates associated with a single application of mesotrione at 150 g ai/ha.

References

Mesotrione (ZA1296): Reduced Risk Rational II, Supplement To MRID: 4405002. Drost, D. Kaminski, B.J., Wheals, I.B., March 1999.

Mesotrione (ZA 1296): 91/414/EEC APPLICATION OF ZA1296 M II Section 5/6

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Registration Status

CALLISTO (480 g/l mesotrione SC) – REGISTRATION TIMELINE USA

Mesotrione is on the EPA's work schedule for review completion by end 3Q01.

Efforts have been made to obtain an expedited review with registration by mid May 2001. The probability of this happening is now very low, although discussions with EPA continue.

Consequently, the GRA position is that registration will only be achieved in time for US sales in 2002.

CALLISTO (100 g/l mesotrione SC) – REGISTRATION TIMELINE EU and Switzerland

Annex I listing in the EU is not anticipated until 4Q01-1Q02.

Provisional approval for a period of 3 years has been obtained in Austria (registration date 16 October 2000) and Germany (registration date 9 November 2000), allowing for sales in the 2001 season.

This formulation has also been granted registration in Switzerland as of 24 January 2001, but this is limited to one year's use (expiry 31 12 2001) on 200 ha until further information on carry-over is produced/submitted.